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Presentation: *New methods for signal detection*

Symposium : *New Methods to enhance drug
safety surveillance.*

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Disclaimer

- The views expressed are those of the speaker and do not represent FDA's policy. References to commercial products are for illustrative purposes only and not an FDA endorsement

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Introduction

- Drug safety data are multivariate and many factors are interdependent
 - Many safety hypothesis cannot be specified a priori
 - Static reports can only give a partial display of the complex relationships
 - In practice, this complexity is difficult to communicate

Improving the detection of rare and serious events

- Traditionally, clinical trials are not powered to detect rare adverse events due to financial and logistic restrictions
- Analysis of frequencies highlights the most common events

- Safety information in medical data bases could be assessed as the data accumulate
- Critical issues could be addressed early and timely and correct adjustments could be made

- In practice, there is a big delay in analyzing data
- More time is spent “cleaning” than in analyzing data (*ST Bennet, JA Adams. Applied clinical trials. 4:44-52, 1995*)
- The cleaning process is complex to document
- The time spent in adapting data and analytical tools is costly

- We reach to information by use of extensive manual configuration and adaptation
- Retrieval of the information is too complicated
- Databases cannot be easily linked
- Integration is complicated
- Information cannot be easily exchanged

Data structures that facilitate automatic analyses

Common data standards will benefit the analyses across all types of medical data, including

- clinical trials
- spontaneous adverse drug reactions databases
- drug exposure
- medical claims
- hospitals medical records
- longitudinal electronic medical records

Self-describing representation of medical data *(Comments by Channing Russell)*

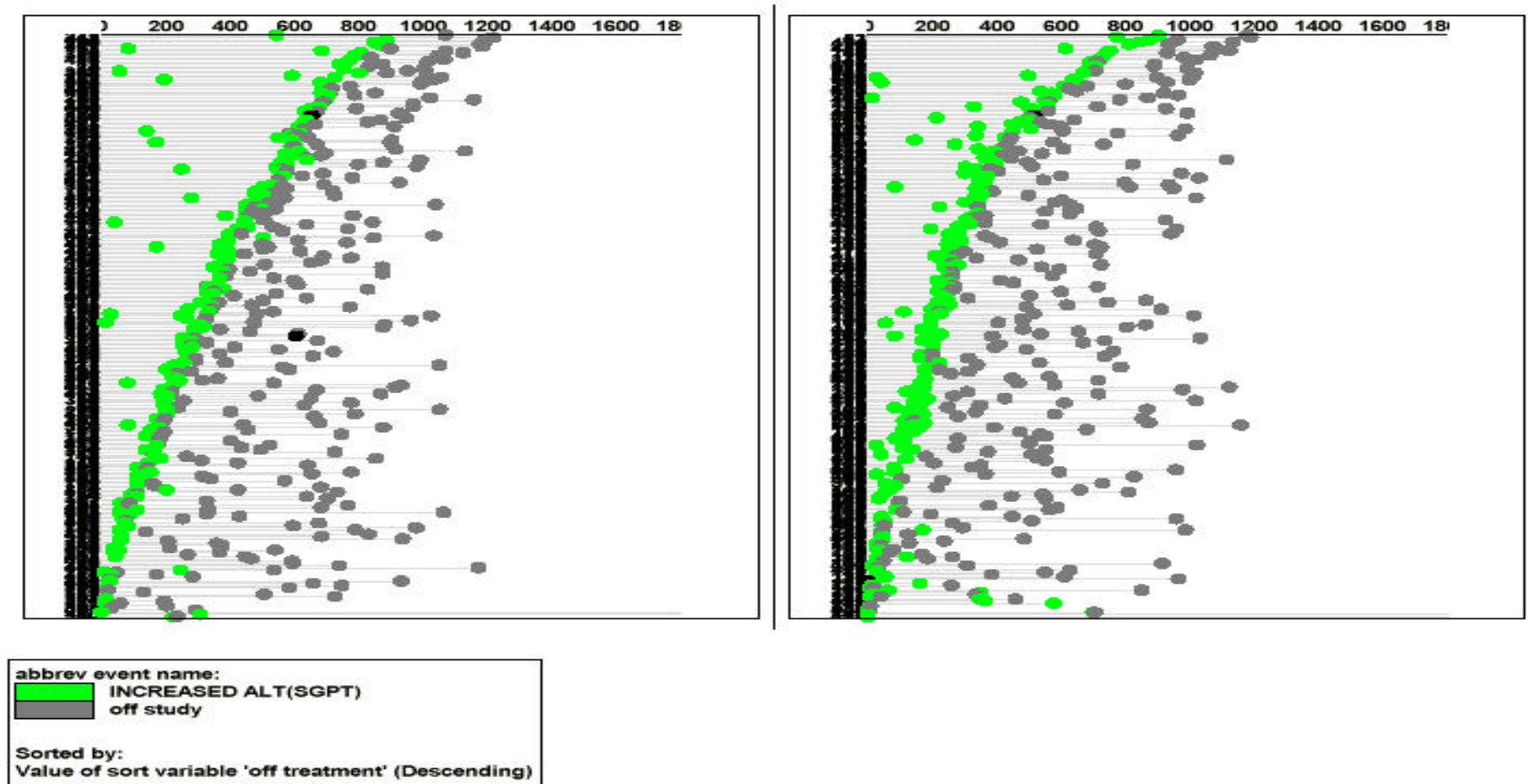
- Will provide substantial help to both sponsors and regulators
- Will reduce
 - the need for study-by-study tool configuration that hinders analysis of safety data
 - the arbitrary differences in clinical data representation
 - unnecessary variability in the sponsor environment
- Will simplify data integration

- We need
 - programs that can identify meanings of common variables *without asking the user*
 - comprehensive metadata of datasets and variables *in human-readable format*
- Common data standards will improve systematic retrieval, analysis, and re-analysis
- Will improve re-examination and reflection on the data already collected

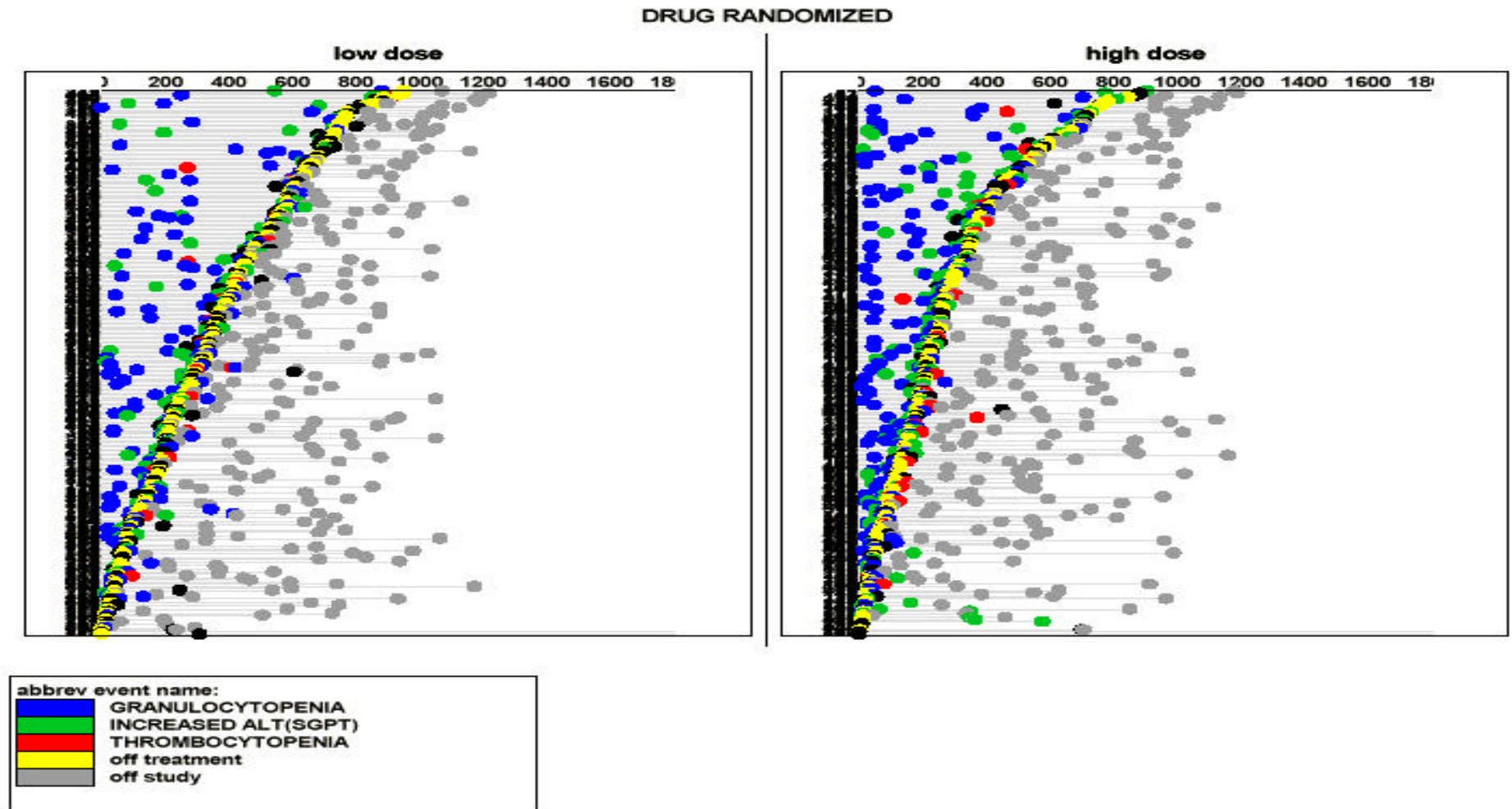
Data integration

- Clinical and laboratory adverse events, medication information, and co-morbidity information
- Inclusion of scheduled and unscheduled clinical laboratory data

Display of the duration of treatment and follow up and the timing of increases in ALT for the 500 patients in a study receiving a "low" and a "high" dose treatment

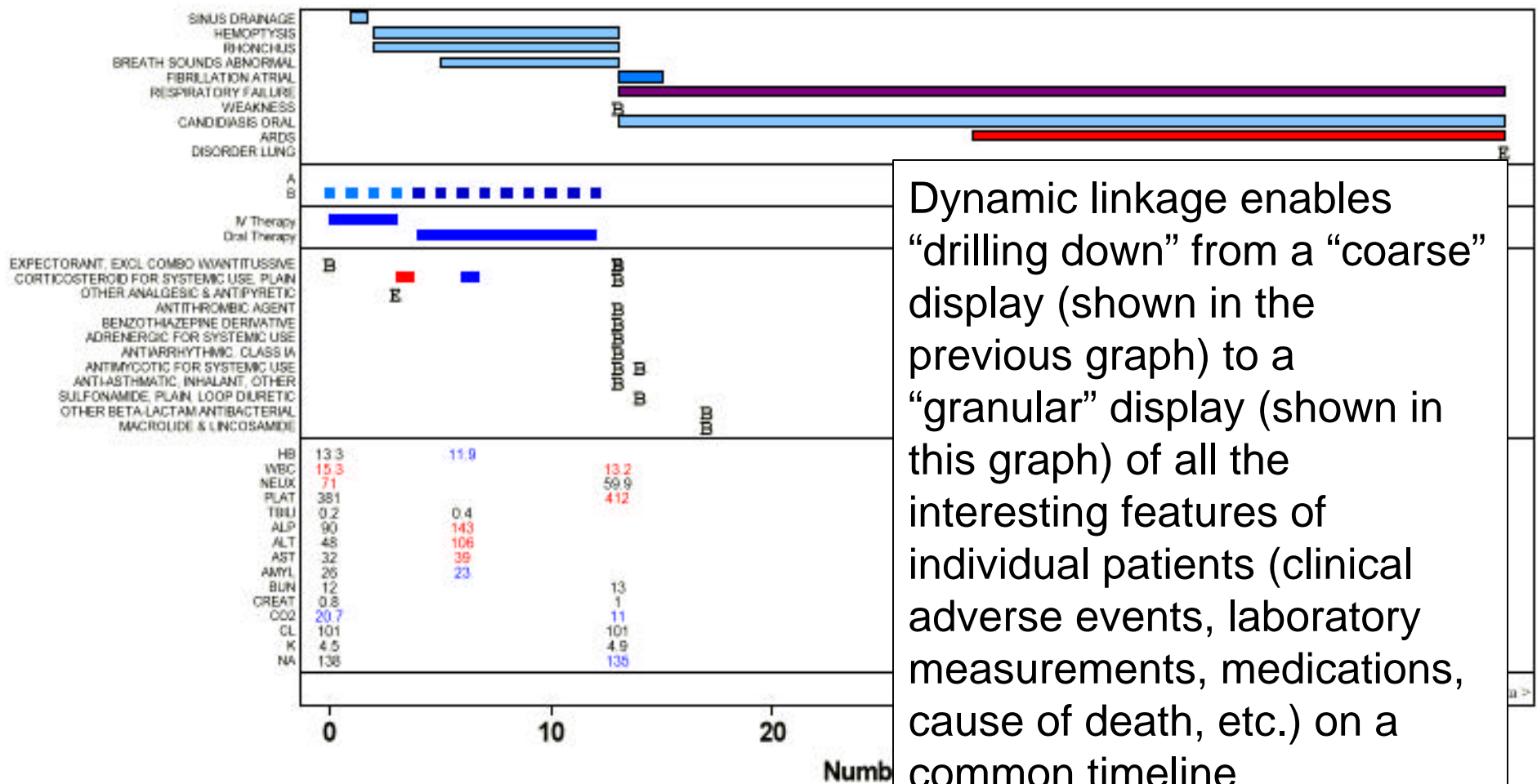


Same patients as before but display of the timing of granulocytopenia, increases in ALT, and thrombocytopenia

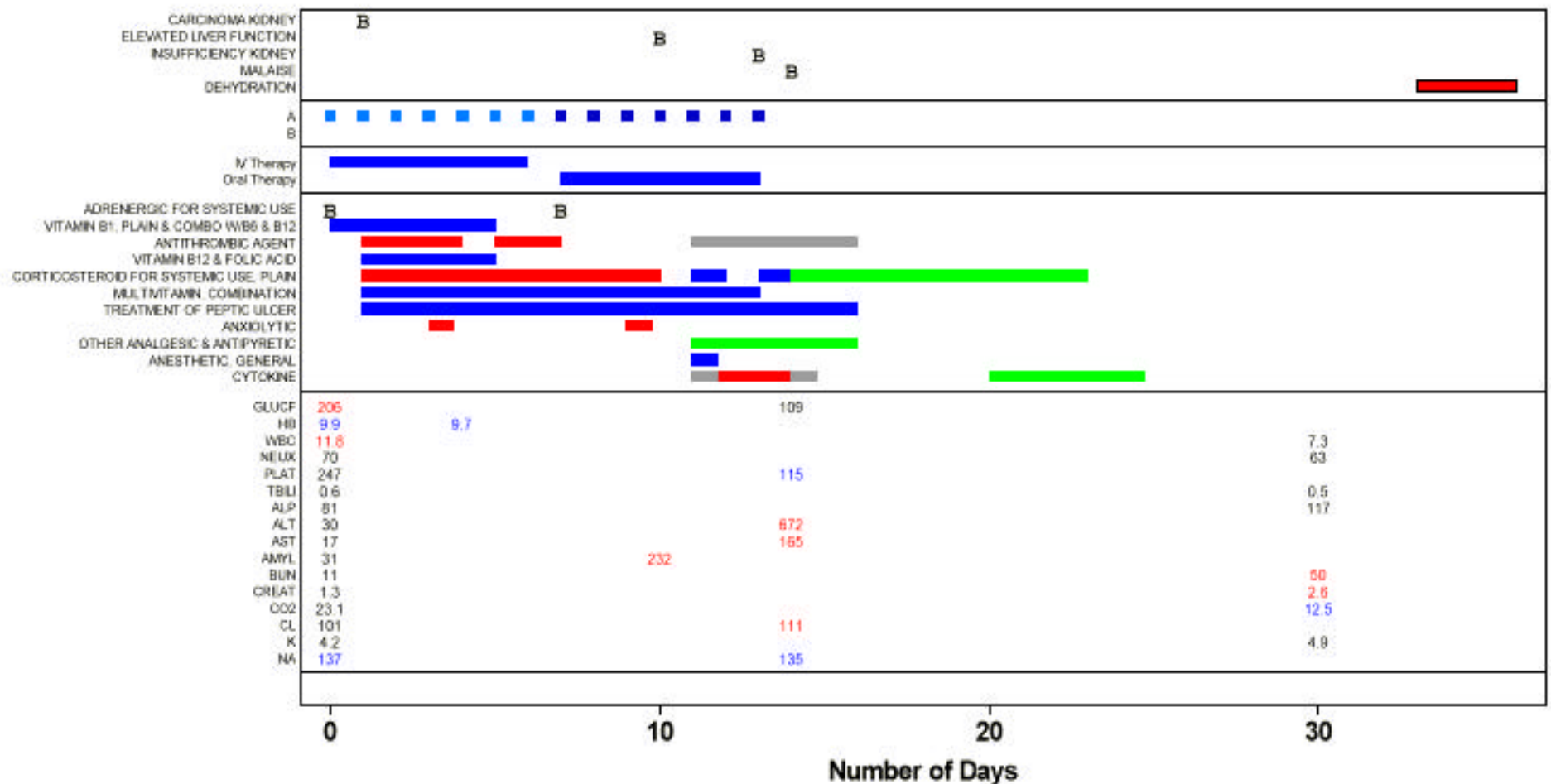


Patient time-line summary graph for Clinical Trial data

AEs, medications, lab results linked on a common timeline



Patient time-line summary graph for Clinical Trial data AEs, medications, lab results linked on a common timeline

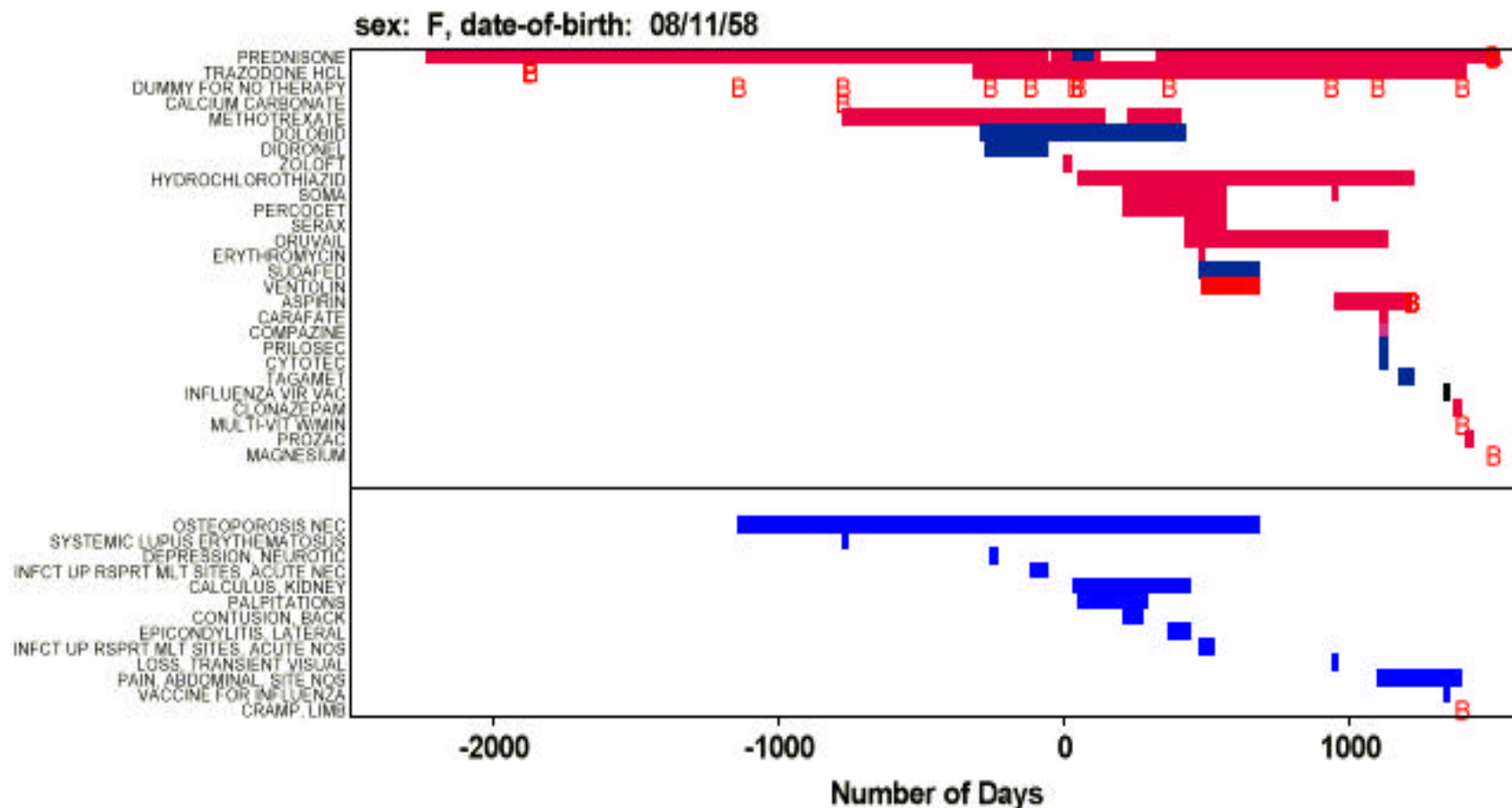


Signal detection based on post-marketing surveillance data

Use of Electronic Longitudinal Medical Records

Patient time-line summary graph for Electronic longitudinal Medical Records Medications and Diagnoses linked on a common timeline

PT_ID
3330



Data mining spontaneous reports

- Principal investigator: Ana Szarfman

The new Data Mining Systems support the following signaling functions

- Detection of "higher than expected" signal scores for
 - Drug-event combinations by drug, drug class, event, event group, and time interval
 - Gender-related drug-event combinations by drug and event
 - Interactions between events and drug pairs

Uncertainties with FDA's post-marketing safety database

- No research protocol that can control for
 - Selection bias
 - Under-reporting
 - Reports enriched in response to publicity or “Dear Doctor” letters
 - Variable historical data
- Some of the data may be invalid: duplications, coding errors, poor quality of information

See more details:

<http://www.fda.gov/cder/adr/>

Impossible to review over 1.8 million records prior to datamining

The challenge of working with this database

- Identification in the vast array of drug-event frequencies,
 - those which are the "interestingly large" frequencies that should be subject to further investigation
- No research protocol

Benefits of working with this database

- Most important of its kind in the U.S.
- Proved its value by identifying and documenting many serious rare adverse drug reactions not identified during randomized controlled clinical trials
- Has a standardized structure
- Over 1.8 million records

Controlling for potential confounding

- Use of stratification
 - There are independent trends that could masquerade as drug-event signals
 - We currently use over 200 strata, including time by 5-year intervals, gender by 3 groups (M/F/U), 10 different age categories, and type of data (SRS or AERS)

The role of stratification by time interval

- Controls for temporal trends in drug usage and for temporal trends in adverse event reporting (independent of drug)
- The time course of safety signals also helps sort out events that are a response to publicity, Dear Doctor letters, etc

The role of stratification by gender

- Controls for gender-based patterns in drug usage and gender-based patterns in adverse event reporting

The role of stratification by age groups

- Controls for drugs with age specific exposure and for events in the same age specific groups

The role of stratification by type of data (SRS or AERS)

- Controls for the use of a new event nomenclature (Meddra) and for the inclusion of more drugs and events per record

Components of the New Systems

A database of all distinct counts of event + drug (or drug pair) combinations derived from the former SRS database and the post October 1997 AERS database

SRS or AERS data extraction

Derived datasets of signal scores

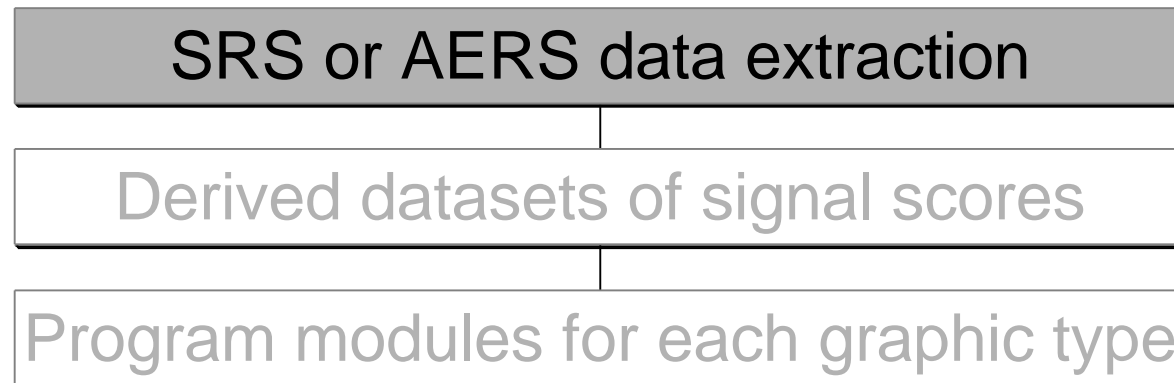
Program modules for each graphic type

New technology: Uses distinct counts of event + drug (or drug pair) combinations to estimate SS derived from application of a statistical model to identify the ones observed at higher than expected frequencies

New technology: A set of pre-programmed graphical displays and modules to explore and examine SS and ancillary data

Components of the New Systems

A database of all distinct counts of event + drug (or drug pair) combinations derived from the former SRS database and the post October 1997 AERS database



Input to systems

- 32 years of data in a standardized structure
- Drugs
 - SRS over 2,500 generic names
 - AERS over 3,000 trade names
- Events
 - COSTART over 1,200
 - Meddra PT over 6,000 event terms

Output from this module

- The frequency of each distinct combination of any drug, event, sex, time, and age group
- Separate outputs for SRS and AERS data

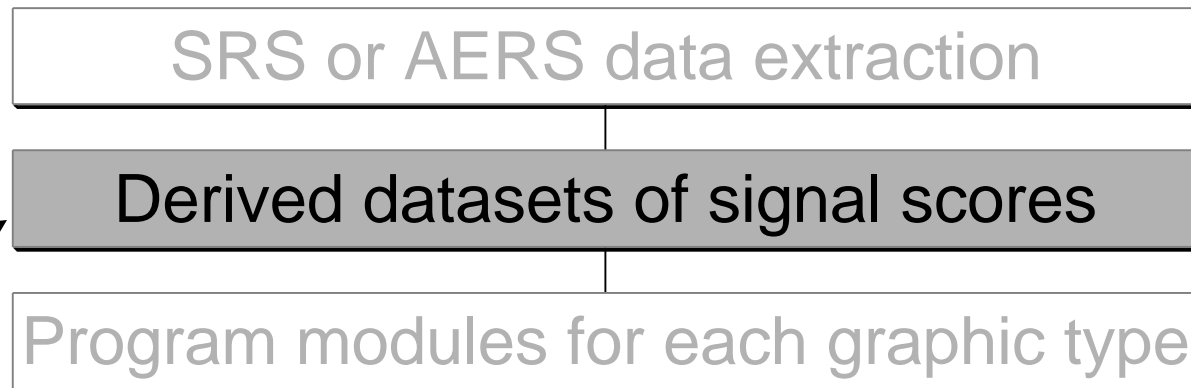
First Lines of the Output

ANALYSIS_NAME	COSTART	SEX	YEAR	AGE_GROUP	count
1,1,1-TRICHLOROETHANE	DEPRESSION	F	5	U	1
1,1,1-TRICHLOROETHANE	DERM CONTACT	M	2	Y16-45	1
1,1,1-TRICHLOROETHANE	DRUG INTERACTION	F	5	U	1
1,1,1-TRICHLOROETHANE	REACT AGGRAV	F	5	U	1
2,2,2-TRICHLOROETHANOL	OVERDOSE	M	2	Y16-45	1
ABCIXIMAB	ABDO ENLARGE	F	6	Y45-65	1

Last Lines of the Output

ANALYSIS_NAME	COSTART	SEX	YEAR	AGE_GROUP	count
ZORUBICIN HYDROCHLORIDE	PHOSPHATASE ALK INC	M	3	Y45-65	1
ZORUBICIN HYDROCHLORIDE	PNEUMONIA	F	4	Y12-16	1
ZORUBICIN HYDROCHLORIDE	POLYURIA	F	6	Y12-16	1
ZORUBICIN HYDROCHLORIDE	SEPSIS	F	4	Y12-16	1
ZORUBICIN HYDROCHLORIDE	SGOT INC	M	3	Y45-65	1
ZORUBICIN HYDROCHLORIDE	WEIGHT DEC	F	6	Y12-16	1

Components of the New Systems



New technology: Uses distinct counts of event + drug (or drug pair) combinations to estimate SS derived from application of a statistical model to identify the ones observed at higher than expected frequencies

D

Derived database of "signal scores"

- Program written by William DuMouchel from AT&T Labs—Research (Dumouchel@research.att.com)
 - *DuMouchel W. The American Statistician, August 1999, Discussion by O'Neill RT, Szarfman A. and others. The American Statistician, August 1999*
- Method appropriately adjusts scores for unstable signals associated with cells with very small expected counts

Notation for counts

- M_i = Total drug frequency
- N_j = Total event frequency
- T = Total database frequency = 5.8 million
- $E_{ij} = (M_i N_j)/T$ = usual statistical Expected frequency analysis for drug-event count
- O_{ij} = Observed drug count
- $S_{ij} = f(O_{ij}, E_{ij})$ = Empirical Bayes "signal score"
- The "signal score" is **DERIVED** from the database
- The score is big if $O \gg E$

The array of drug-event combination cells is vast

- Many cells are empty cells (drug-event combinations that do not exist)
- Many cells have very small expected frequencies
- ***This has always posed many analytical problems***

Properties of the computations of "signal scores"

- Stratification of calculation of the E_{ij} by gender, time, age groups, and SRS and AERS
- A model **DERIVED** from the data "shrinks" (adjusts) "unstable" O/E and ranks "'interesting' signal scores"
- This adjustment dampens "unstable" O/E (E_{ij} too small (0.001) due to small M_i and N_j)
- Method picks out O/E ratios much larger than 1

Counts

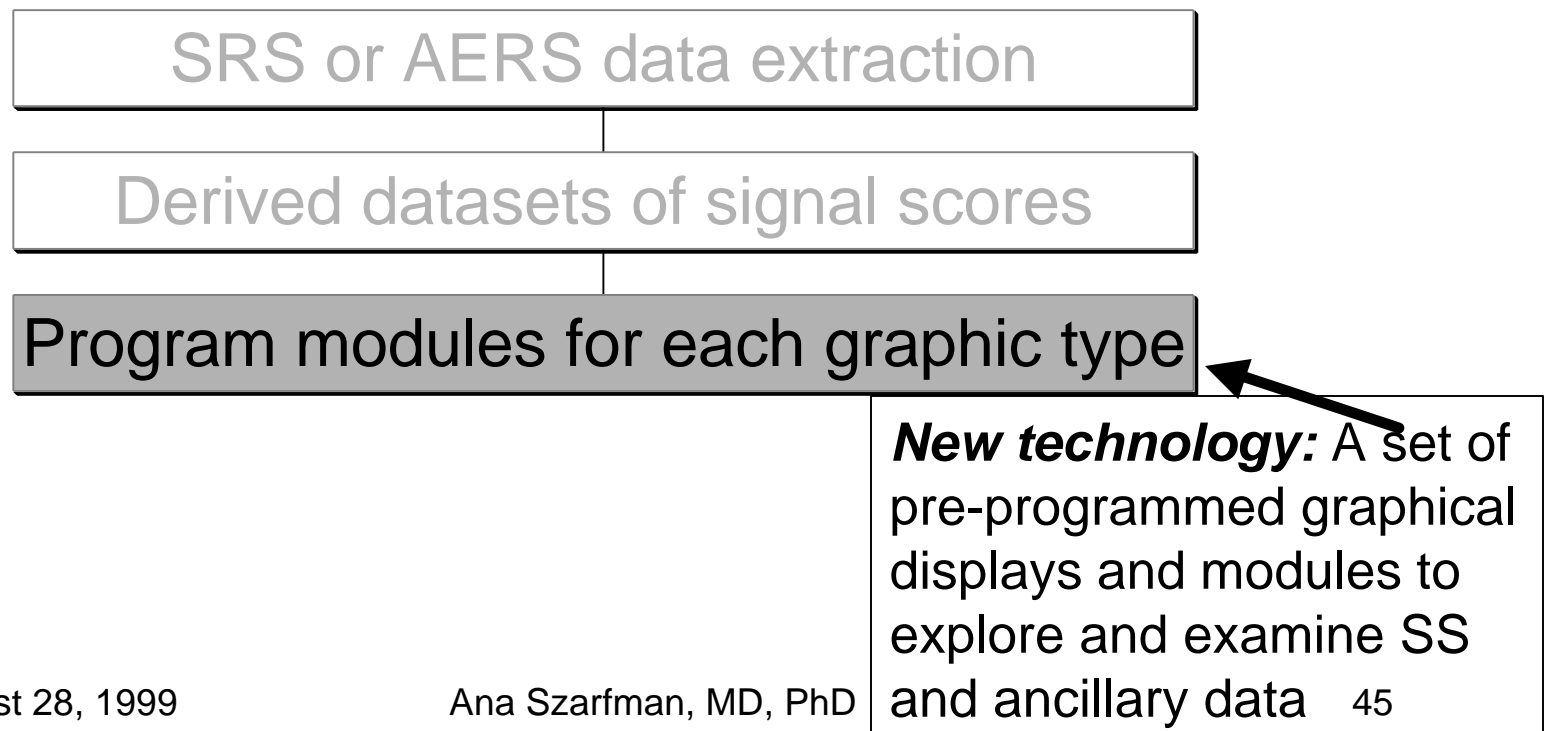
- SRS (1968-October 1997)
 - 5.8 million
- AERS (Post-October 1997)
 - 2.4 million
- Counts per gender
 - SRS total frequency count 5 . 8 million
 - Female 3 . 2 million (58%)
 - Male 2 . 3 million (42%)
 - Unknown 0 . 3 million

*(A similar F/M proportion is generally seen in drug utilization data**
(↑ with antidepressants, ↓ with aspirin)

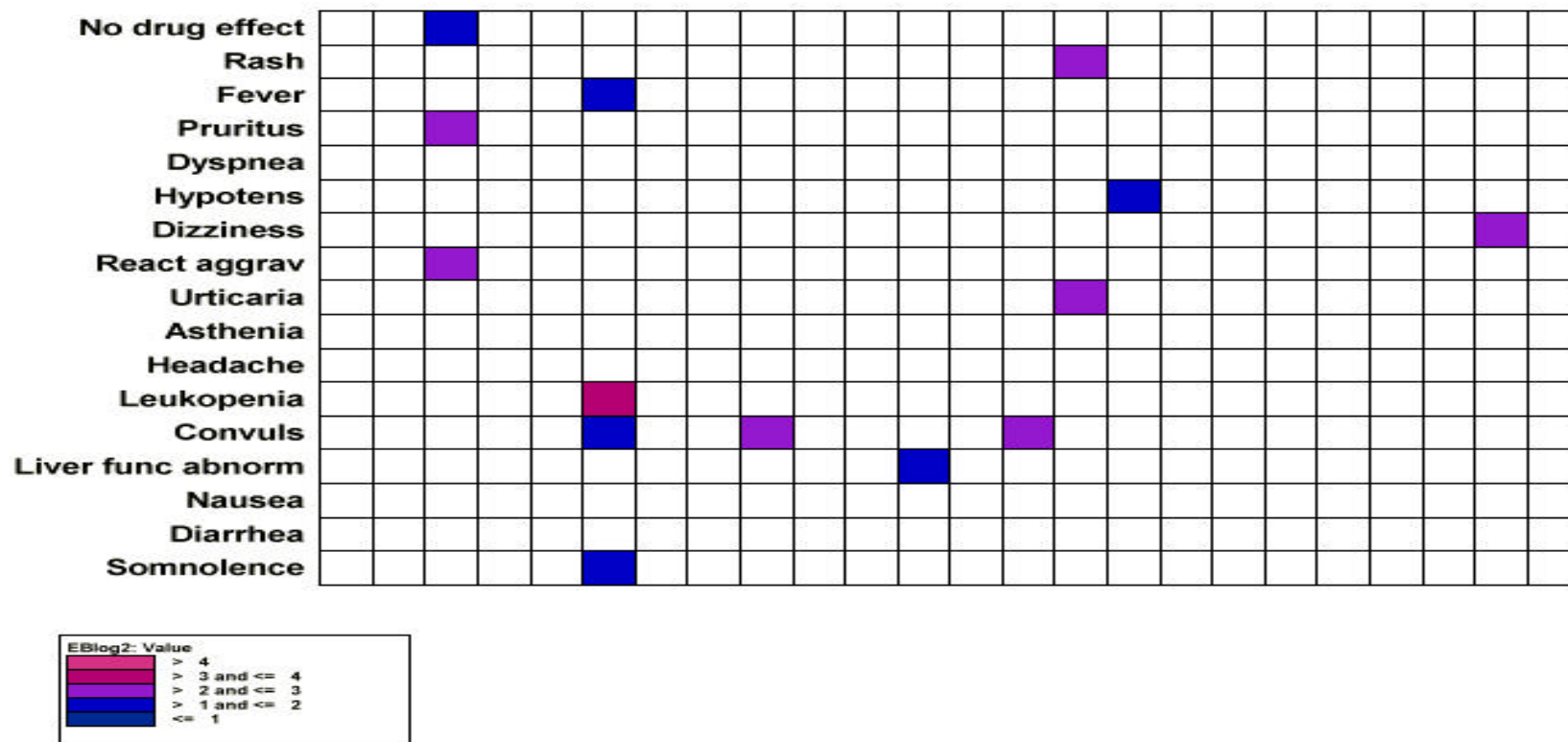
First Lines of the Output

Rank	ANALYSIS_NAME	COSTART	N	E	RR	EBGM
1	IOPHENDYLATE	ARACHNOIDITIS	309	0.283102	1091.48	852.92
2	ROPIVACAINE	LABOR ABNORM	63	0.04033	1562.1	526.31
3	FACTOR IX COMPLEX	HIV SYND	205	0.352493	581.57	474.63
4	ETIDOCAINE	TRISMUS	84	0.129145	650.43	402.55
5	PHENIRAMINE	MYDRIASIS	125	0.235948	529.78	396.22

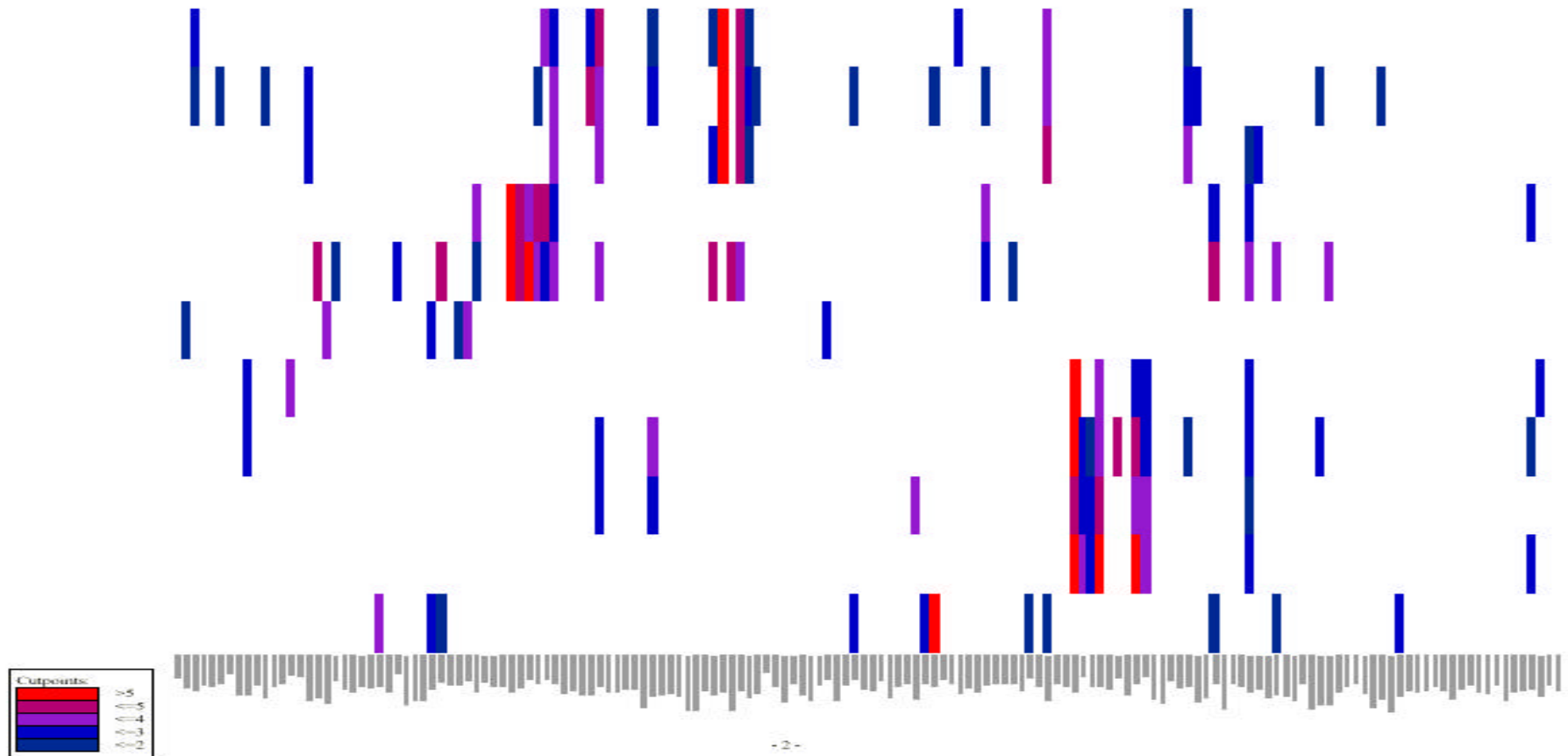
Components of the New Systems



Spatial map showing the signal scores for the the most frequently reported events (rows) and drugs (columns)



Spatial map showing fingerprints of signal scores for drugs (rows) associated with specific events (columns)



Signal scores, number of reports, and events (rows) associated with a specific drug according to the years (columns) when the first signal was detected

TOP PANEL: New method:

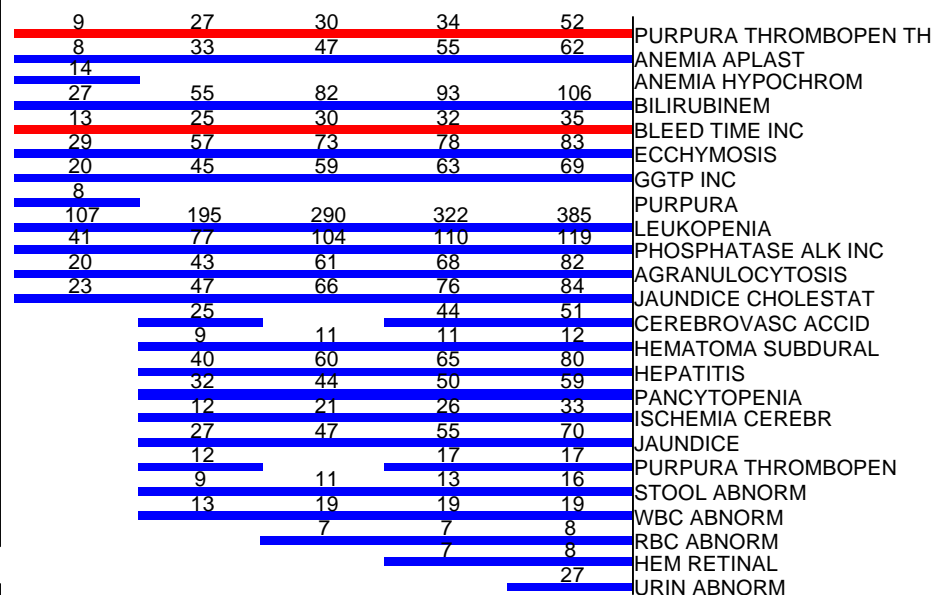
Timing (x-axis) of all events that generated signals (y-axis)

Color-coded scores (from highest to lowest): red ≥ 4 , blue < 4

Numbers: number of reports for each interesting score

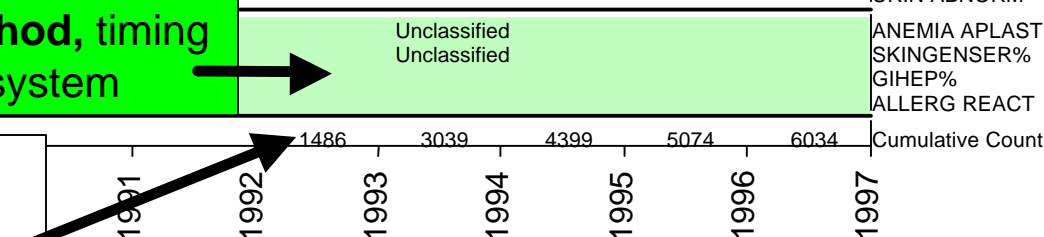
Events are sorted by time of detection

Filter: scores > 2 & $N > 6$

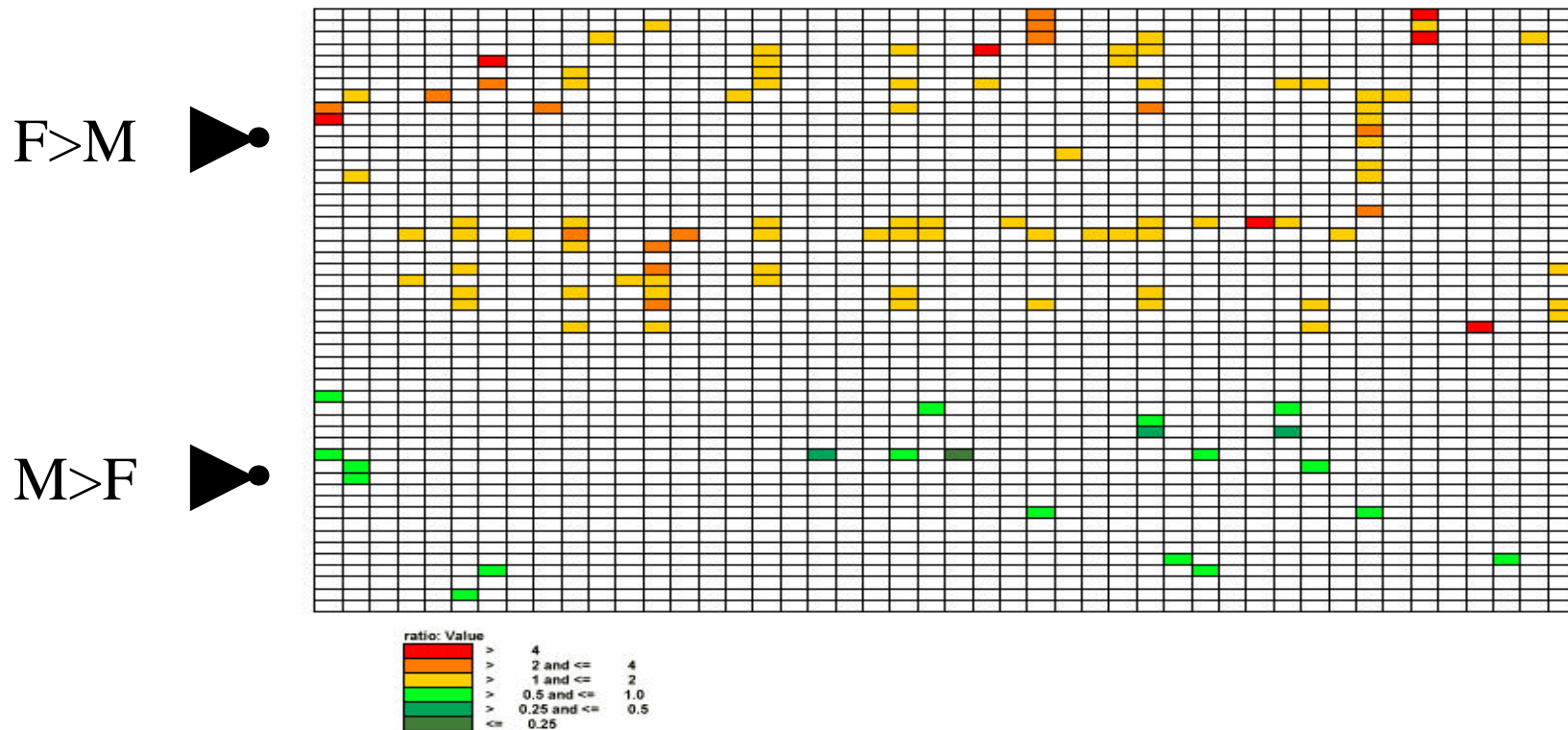


MIDDLE PANEL, Current method, timing of signals in the MAR tracking system

BOTTOM PANEL: New method, cumulative number of reports



Spatial map showing fingerprints of signal scores for specific events by gender (rows) and the associated drugs (columns)

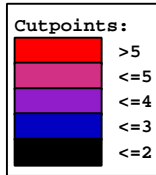


Process of validation

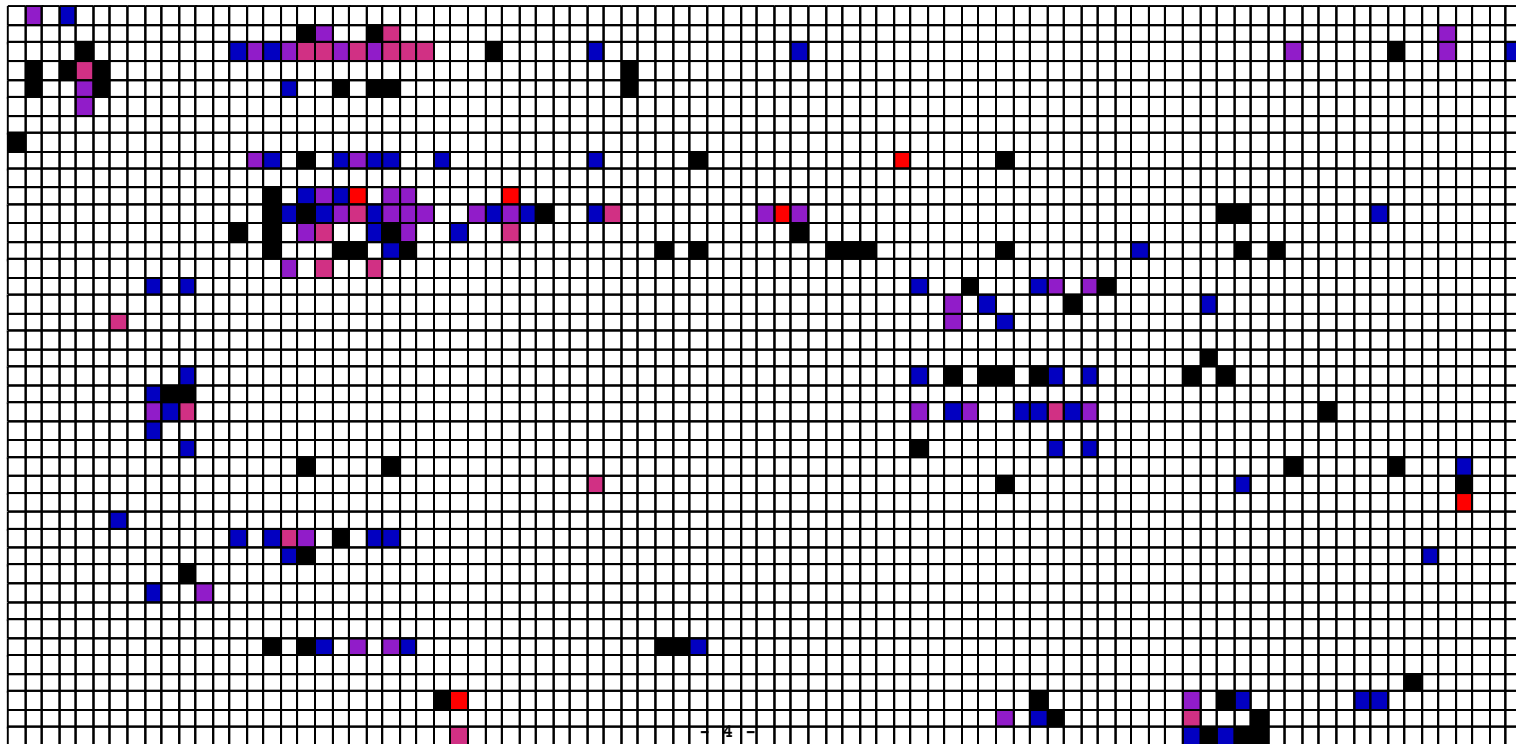
- We validated this approach using positive and negative controls and by picking up rare events earlier than with current methods
- Signals are routinely examined for consistency among drugs of similar chemical structure or among related adverse events

- Positive associations included
 - drug-events that lead to removal of drugs from the market or that
 - required labeling changes, and
 - signals identified by using routine methods
- Negative associations were identified
 - by comparing drugs in several drugs classes used to treat the same indications
 - identifying that signals characteristic of one class of drugs were absent in the other classes

Spatial map showing the positive and negative events (columns) among NSAIDs grouped by class (rows) by the intensity of SS (color) (page 4 of 9). These results confirm previous medical knowledge



Marketed



Strengths of the systems

- Allow to look across all the data
- The huge size of this database and the use of this new methodology enable multiple comparisons and probing for consistency and replication across groups of events and classes of drugs
- Very sensitive in detecting safety signals associated with a small number of reports

Important considerations

- Signals detected include condition being treated (*lack of effect* and its variations is one of the most common complaints)
- Need expertise of Safety Reviewers and Medical Officers to analyze and interpret the data

Determination of the labeling status of an adverse event

- Safety analyses require knowing the "labeled" versus "unlabeled" status of drug-event combinations
- The events need to be efficiently extracted from the free text in package inserts and used to filter known signals

Conclusions

- Data standardization will simplify the systematic analysis of safety data
- We will continue making progress in the drug safety area
 - The correlation between adverse event activity and chemical structure will help predict the toxic potential of new drugs
 - The identification of drug metabolism phenotypes will help predict patients at risk

References (updated January 2,000)

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